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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/090,320	03/01/2002	Yanxiang Cao	3446	5376

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AFFYMETRIX, INC
ATTN: CHIEF IP COUNSEL, LEGAL DEPT.
3380 CENTRAL EXPRESSWAY
SANTA CLARA, CA 95051

EXAMINER	
ZHOU, SHUBO	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/090,320	CAO ET AL.	
	Examiner	Art Unit	
	Shubo (Joe) Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/9/02, & 5/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Amendments

1. Applicants' election, without traverse, of Group I (claims 1-29, 31-40), filed 7/14/04, is acknowledged.

Claim 30 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the paper filed 7/14/04.

Accordingly, claims 1-40 are currently pending, and claims 1-29, and 31-40 are under consideration.

Information Disclosure Statement

2. The information disclosure statements filed 7/9/02 and 5/28/04 respectively are acknowledged and references therein have been considered. A copy of the signed PTO-1449 is attached.

3. The citations/listings of publications and/or patents in various sections of the specification such as those on page 2 and elsewhere are not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

4. The specification is objected to because of the following:

Applicant is reminded of the proper content of an Abstract of the Disclosure. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. In the instant case, the Abstract on page 32 of the specification does not give the use(s) of the claimed methods. Complete revision of the content of the abstract is required on a separate sheet.

The status of the nonprovisional patent application (whether patented or abandoned) in the specification, such as that under the priority claim on page 2 of the specification, should be updated. If a patent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the application. If a patent application has become abandoned, the expression "now abandoned" should follow the filing date of the application. It is noted that priority claims to prior applications are included in the ADS filed 3/1/02, thus, the priority claim is not required to appear in the first sentence of the specification. However, if applicants choose to keep the priority claim in the first sentence of the specification, the sentence should be amended so that the relationship between the instant application and the prior application 09/641,081 is clearly indicated.

It is noted that trademarks are used in this application, such as GENECHIP™ (registered by Affymetrix Inc.) on page 10. Trademarks should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

5. Appropriate correction is required.

Claim Rejections-35 USC § 112

6. The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

7. Claims 7-9 are rejected under 35 U.S.C. 112 , second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-9 recite the phrase "3' region" and/or "5' region" of an RNA molecule. The metes and bounds of the limitations are not clear. For a given RNA molecule, absent a clear definition in the specification, it is not clear precisely what the boundaries of the 3' region and the 5' region are.

Further, the meaning of the limitation, in claim9, "the molar amount of cDNA fragments that hybridize to a probe to a 3' region of a RNA and the molar amount of cDNA fragments that hybridize to a probe to a 5' region of said RNA vary by 2 fold or less" is unclear. For the sake of explanation, the limitation can be shortened as "the amount of X and the amount of Y vary by 2 fold or less". The limitation, as currently

written, is interpreted that the sum of the amount of X and Y varies by 2 fold or less, but it is not clear relative to what is the 2 fold or less variance. If applicants intend that the amount of X over the amount of Y varies by 2 fold or less, the claim should be so amended.

8. Clarification of the metes and bounds of the phrases are required.

Claim Rejections-35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-4, 6-29, and 31-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al. (US Patent No. 6,040,138, Date of Patent: Mar 21, 2000, filing date: Sep. 15, 1995) in view of Gibco BRL (Superscript™ Choice System

for cDNA synthesis, Gibco BRL Catalog and Reference Guide, 1992) and Pharmacia Biotech (Molecular and Cell Biology Product Catalog, 1994), and further in view of Williams et al. (Nucleic Acids Research, Vol. 22, pages 1365-1367, 1994).

The claims are drawn to a method of analyzing an RNA sample comprising converting the RNA into cDNAs with random primers and reverse transcriptase, which cDNAs are then hybridized to nucleic acid probes on a solid support. The method comprises fragmenting the cDNAs for labeling.

Lockhart et al. teach a method of monitoring gene expression by hybridization of cDNAs derived from total RNA or mRNAs of biological samples by reverse transcription using oligo dT primers to high density oligonucleotide arrays. See columns 4, 11, 12. However, Lockhart et al. do not explicitly teach that random primers are used for the reverse transcription and the cDNA synthesized for hybridization to the probes on the array are fragmented.

Both Gibco BRL and Pharmacia provide commercial kits for synthesizing cDNA from RNA for various purposes. Gibco BRL provides Superscript Choice System for cDNA Synthesis comprising both oligo dT primers and random hexamers. The instruction teaches that the primers can be used individually or together. See page 368 and the illustration on page 369. Pharmacia provides TimeSaver cDNA Synthesis Kit comprising both Oligo dT primers and random hexamers. The instruction teaches that random primers are useful for making cDNAs that increase the representation of 5' end of an RNA, or for copying mRNAs lacking a poly(A) tail.

Williams et al. teach that dangling ends of a duplex formed by the hybridization of the two oligonucleotides have unpredictably effect on the stability of the duplex, depending on the location and composition of the dangling ends. See Abstract, page 1365, Figure 1 on page 1366, and the Discussion on page 1367.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Lockhart et al. to use random primers in lieu of, or in addition to the oligo dT primers to take advantage of using random primers in reverse transcription so that the cDNA produced have a better representation of the 5' end of an RNA molecule. One having ordinary skill in the art would also have been motivated by Williams et al. to modify the method of Lockhart et al. to fragment the cDNAs before labeling to generate labeled cDNA fragments that are similar to the lengths of the probes on the oligonucleotide array in order to minimize the dangling ends of the duplex formed after hybridization so that a better consistency can be achieved as to the signal intensities obtained from a sample and/or among multiple samples.

As to claims 2, 7, 8, and 9, which require that the number of cDNA copies of a given sequence near the 3' end of an RNA is not more than twice the number of cDNA copies of a given sequence near the 5'end of the RNA molecule, or that the hybridization signal detected with a probe to a 3' region of an RNA is not more than twice the amount of signal detected with a probe to a 5' region of the RNA, it would have been obvious to a person having ordinary skill in the art at the time the invention was made that since the random primers used for priming the RNA into cDNA would be relatively uniformly distributed to an RNA molecule during reverse transcription, and as suggested by Pharmacia that the use of random primers increases the representation of the 5' end of an RNA molecule, the number of cDNA copies of a given sequence near the 3' end of the RNA would not be more than twice the number of cDNA copies of a given sequence near the 5'end of the RNA molecule, hence the hybridization signal detected with a probe to a 3' region of an RNA would not be more than twice the amount of signal detected with a probe to a 5' region of the RNA.

As to claims 3, 10, 15-20, 32-36, and 38-39, which requires the RNA sample comprises a particular type of RNA or from a particular source, Lockhart et al. teach that

the RNA sample can be total RNA, or mRNA or poly(A)+ RNA. See columns 2-3, 10 and 11. Further, Lockhart et al. teach that the RNA sample can be from any organism, any biological tissues or cells, or clinical samples, or sections of tissues or frozen sections. See columns 11-12.

As to claim 14, which requires that the RNA sample is isolated from a prokaryotic cell, a person having ordinary skill in the art would have been motivated to use the method of Lockhart et al. and use random primer for the synthesis of cDNA from RNA of a prokaryotic source because Lockhart et al teach that their method can be used for RNA samples from any source (see above), and Pharmacia teaches that reverse transcription with random primer would be useful for copying mRNA lacking a poly(A) tail, which is the case for prokaryotic RNA.

As to claims 11-13, which require that the random primers used for reverse transcriptions are 6, 9, or 15 nucleotides in length, it would have been obvious to one of ordinary skill in the art that the exact length of the random primer can vary in the cDNA synthesis because different length of random primers have been used in the prior art. For example, the kits of Gibco BRL and Pharmacia comprise random hexamers (6mer); Malfroy-Camine et al. (US 5,780,025, date of patent: Jul. 14, 1998) teach using random octamers in the synthesis of cDNA from RNA (see column 17); and Lader et al. (US 6,057,134) disclose using random decamers for reverse transcription to synthesize cDNA (see column 6). Thus, one of ordinary skill in the art would be motivated to try various lengths of random primers such as, 6mers, 9mers or 15mers to see whether better synthesis would be achieved.

11. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al. (US Patent No. 6,040,138, Date of Patent: Mar 21, 2000, filing date: Sep. 15, 1995) in view of Gibco BRL (Superscript™ Choice System for cDNA synthesis, Gibco BRL

Catalog and Reference Guide, 1992), Pharmacia Biotech (Molecular and Cell Biology Product Catalog, 1994), and Williams et al. (Nucleic Acids Research, Vol. 22, pages 1365-1367, 1994), as applied to claims 1-4, 6-29, and 31-40 above, further in view of Gibco BRL (Terminal Deoxynucleotidyl Transferase, Gibco BRL Catalog and Reference Guide, 1992).

The claim is drawn to a method of analyzing an RNA sample comprising converting the RNA into cDNAs with random primers and reverse transcriptase, which cDNAs are then fragmented and labeled by the addition of at least one labeled nucleotide using terminal transferase before being hybridized to nucleic acid probes on a solid support.

Applied to claims 1-4, 6-29, and 31-40 above, Lockhart et al., Gibco BRL and Pharmacia Biotech teach or suggest a method of monitoring gene expression by hybridization of cDNAs derived from total RNA or mRNAs of biological samples by reverse transcription using random primers to high density oligonucleotide arrays. However, the references do not explicitly teach that the cDNA fragments are labeled by the addition of at least one labeled nucleotide using terminal transferase.

Lockhart et al. teach that the labels of the cDNAs can be made with any of the means known to those of skill in the art such as end labeling.

Gibco BRL discloses and provides a terminal deoxynucleotidyl transferase. The instruction for the product states that the enzyme is "suitable for adding momopolymer tails to the 3' end of DNA" or "for labeling the 3' ends". See page 290.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Lockhart et al. to use terminal transferase to end label the cDNA fragments because Lockhart et al. clearly motivates and suggests end labeling and Gibco BRL provides the terminal transferase enzyme for exactly this purpose.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on 571-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549.

14. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center

supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shubo (Joe) Zhou, Ph.D.

Patent Examiner

16 October 2004

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER